Is QT Prolonged or Shortened? Normal Limits.

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This communication is limited to three considerations: 1) QT adjustment for rate and gender; 2) Upper and lower normal limits for rate- and gender-adjusted QT; and 3) Evaluation of QT shortening and prolongation. The data in this communication is also primarily restricted to QT data in populations investigated by the author personally.

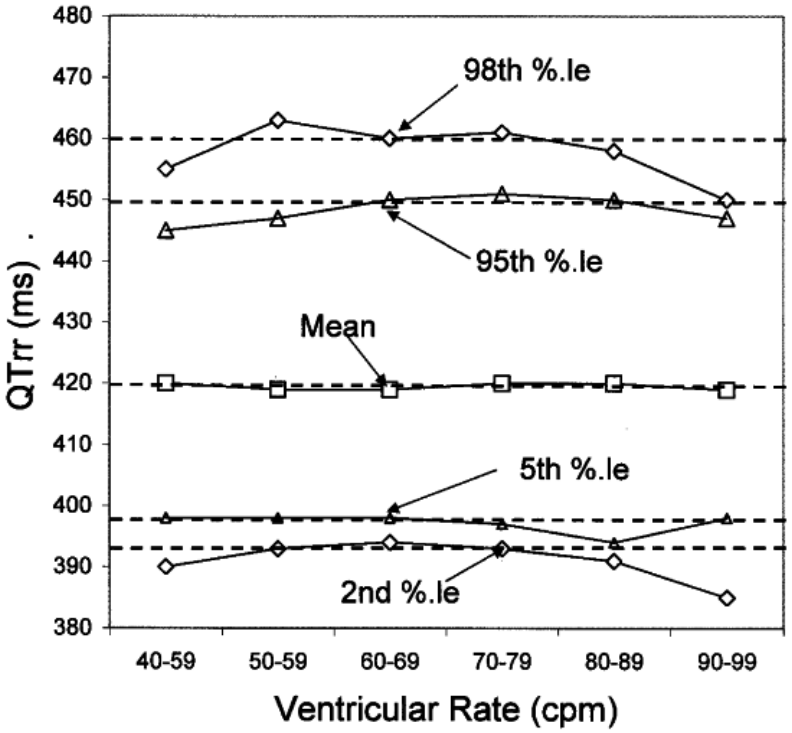

Figure 1. Normal limits for QT adjusted for rate and gender as a linear function of RR (QTrr) according to Equation [1] from a group of 6,977 normal adult women for various subintervals of ventricular rate. Graphed from normal population in Chapter 11 in reference (1).

QT adjustment for rate and gender

Equation [1] gives a practical common formula for QT rate- and gender adjustment in adult men and women 40 years old and older. A comparison of the display of gender-specific normal limits for QTrr in various ranges of ventricular rate in normal women (Figure 1) and in normal men (Figure 2) shows that the gender differences after gender adjustment in men by 6 ms are quite small throughout the physiological range of ventricular rates.

[1] $QTrr = QT + 184*[1 - RR]$ in women, and

[2] $QTrr = QT + 184*[1 - RR] + 6$ ms in men aged 40 years and older;
$+ 12$ ms in younger adult men.

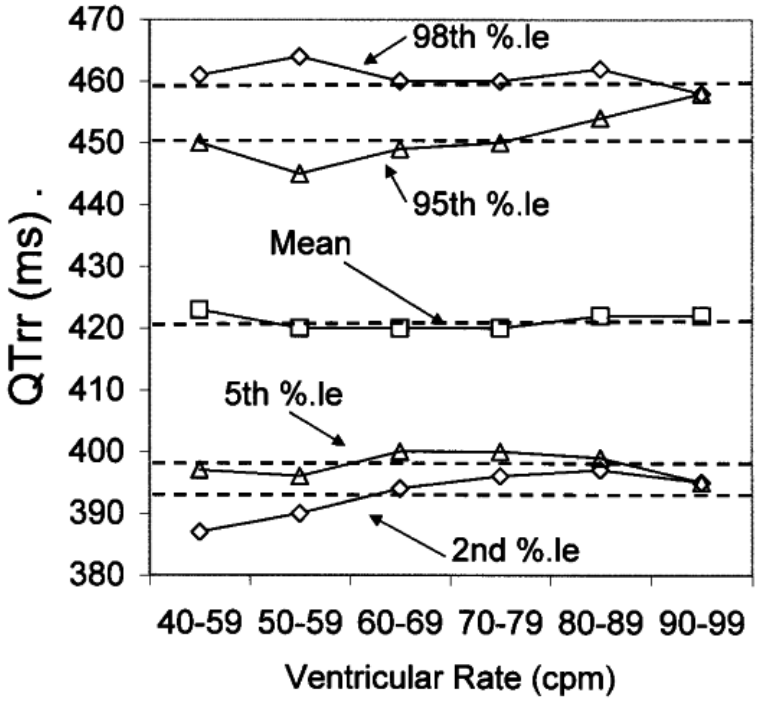

Figure 2. Normal limits for QT adjusted for rate and gender as a linear function of RR (QTrr) according to Equation [2] from a group of 4,742 normal adult men for various subintervals of ventricular rate. Graphed from normal population in Chapter 11 in reference (1).

The values of the slope coefficient varies to some extent in various race- and gender-specific formulas in these normal populations sampled and evaluated using identical procedures under strict quality control. In general however, these differences are relatively minor compared to values obtained with common QT adjustment functions from a pooled sample of these populations (1-3). These large normal groups included over 10,000 white and African-American men and women (1,2). In addition, a group of over 20,000 racially more diverse women selected with strict criteria for normality were chosen for determination of normal values for QT and QT subintervals (3).

The value of the slope coefficient differs from the values in Equations [1] and [2] when QT adjustment functions that are functionally different from equations [1] and [2] (for instance the Bazett's formula) are used(2). They are

more similar when structurally similar, linear regression functions are used (4), although even in some large population samples substantially lower values for slope coefficients have been found [5], possibly reflecting a wider scatter and lower correlation in the QT/RR relationship.

Upper and lower normal limits for normal QT derived from normal populations cited above are listed in Tables 1 and 2.

Table 1. Upper Normal Limits in Adult Men and Women for Ventricular Rates from 45 to 100 cpm

- Upper 5th Percentile Normal 450 ms
- Upper 2nd Percentile Normal 460 ms

Table 2. Practical Limits for Short QT in Adult Men and Women

- Lower 5th Percentile Normal 400 ms
- Lower 2nd Percentile Normal 395ms

Dependence of normal limits on the definition of "normal."

Exact values of normal limits for rate-corrected QT depend on the characteristics of the populations used for determination of normal limits. In general, the stricter the selection and exclusion criteria, the lower the upper normal limits. Figure 3 illustrates that the upper normal limits in women were approximately 10 ms lower than those listed in Table 1 when exclusions included those with any adverse cardiac events during the follow-up in addition to history, clinical and laboratory data and information on utilization of cardioactive drugs. These still relatively minor differences in normal limits probably reflect the fact that even smaller degree of QT prolongation indicates increased risk of adverse cardiac events. It is also noted that the lower normal limits in these adult "supernormal" women were

approximately 5 ms lower than those listed in Table 2. Overall, it is practical to take rate-adjusted QT values 460 ms or longer as a sign of definite QT prolongation.

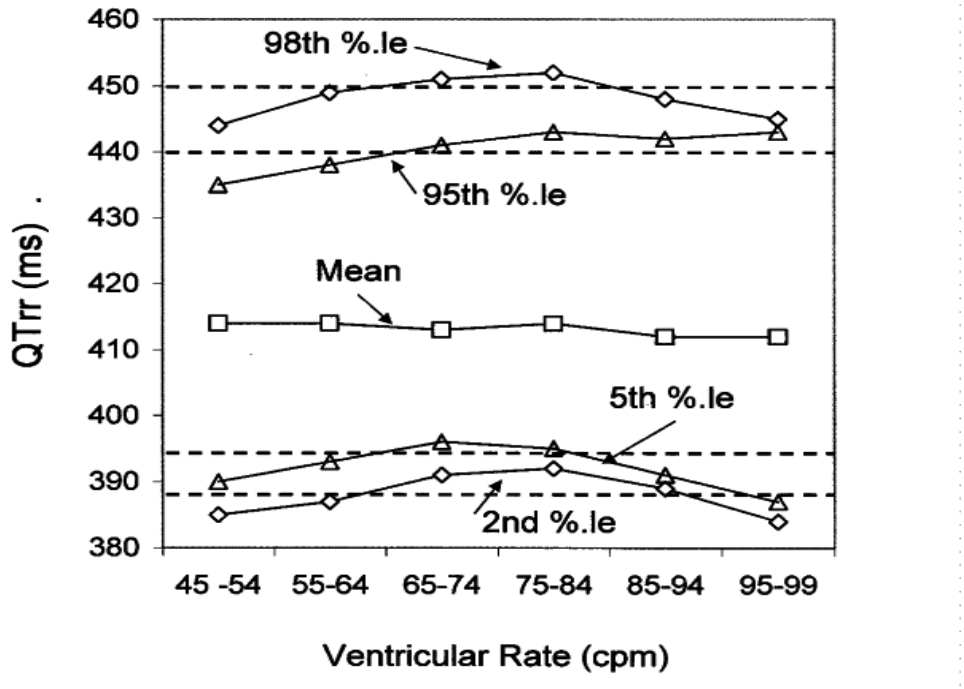

Figure 3. Upper and lower percentile normal limits for QTrr in various ranges of ventricular rate determined in a group of over 23,000 normal women. The upper normal limits are 10 ms lower than in other normal groups in this female group screened carefully for health status, including absence of adverse cardiac events in 6.3 year follow-up 10 ms lower than in other normal groups. Graphed from data of population in reference (3).

Table 3. Conditions for Validity of Normal Limits

- Ventricular rate is within physiologically normal limits (45 cpm to 95 cpm)
- Rate and gender adjustment is done properly
- QT measurement and measurement validation is done properly

No general QT adjustment functions are valid if the ventricular rate is 110 cpm or higher. Caution should be exercised in using any normal QT limits in arrhythmic conditions like atrial fibrillation with large variations in ventricular rate.

NOTE: Normal limits published in the literature have been frequently derived as (mean +/- 2 SD). Such limits may be misleading because of variably skewed QT distributions in various ranges of the heart rate (2).

Background of rate and gender adjustment

There are several possible appropriate QT prediction functions. In general, they are of the form:

[3] $QT = k1*RR^x + k2$,

where RR^x is some power of the RR interval and k2 is the regression intercept.

NOTE: The exact form of the rate variable such as various power functions of the RR interval (RR^x) is relatively unimportant. The evaluation of various power functions in terms of their prediction accuracy (R-square values) reveals that they are all within 1 ms for RR with exponents (x) ranging from 1/3 (Fridericia) to 1 (linear function) (2,6), provided that they are properly used with considering the intercept k2.

The primary source of errors is the omission of the intercept from the prediction equation and the corresponding QT rate adjustment function (1). No single normal limit is valid if the intercept is omitted. The reason is as follows:

Taking the exponent (x) of RR for instance as 1/2, Equation [3] becomes

[4] $QT = k1* RR^{1/2} + k2$

If both sides of Equation [4] are divided by $RR^{1/2}$, we get

[5] $QT / RR^{1/2} = k1 + k2 / RR^{1/2}$

Equation [5] shows that the Bazett's formula (the left side) is not equal to a constant k1 but in addition, it retains an error term [$k2 / RR^{1/2}$]

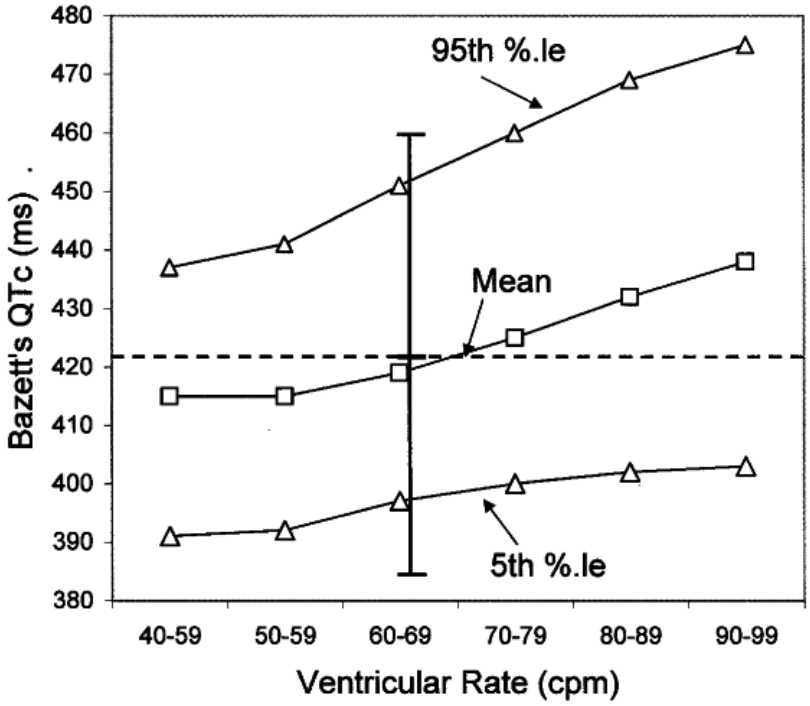

Figure 4. Bazett's QTc in 11,739 normal adult subjects with upper and lower 5th percentile normal percentile limits by ventricular rate. A strong dependence of QTc on ventricular rate is noted (r = 0.31). The vertical bar indicates the normal range as commonly estimated (mean QTc +/- 2SD). QTc produces false QT prolongations or missed true prolongations if ventricular rate in any given subject deviates from 60 cpm or if ventricular rate differs between the control and treatment groups in drug trials. Graphed from normal population in Chapter 11 of reference 1.

Figure 4 graphed from recalculated data from the normal population of men and women from reference (1) shows that the commonly used upper normal limits for QT are not valid if the ventricular rate deviates from 60 cps. The residual correlation of QTc with heart rate is quite high (r= 0.32).The error is substantial for the higher normal limits and somewhat smaller for the lower normal limits. The use of Bazett's QTc can result in false QT prolongations or missed true QT prolongations if ventricular rate deviates from 60 cpm. These problems may also go unnoticed in serial comparisons if an individual's ventricular rate changes between the baseline and follow-up, or if ventricular rates differ between the control and treatment groups in drug trials.

Limits for QT prolongation in children.

Normal limits for QT interval in children have been published for the Bazett's formula by Risnbeek et al. (7). These authors listed the medians and the upper and lower second percentile limits in various age subgroups from birth to 16 years in a relatively large study group (944 males and 968 females). The upper normal limit of QTc within age range from 1 year to 12 years stays within 445 and 455 ms. The data suggest that QTc exceeding 460 ms is clearly prolonged at any age from birth to 16 years .

The limitations of the Bazett's formula should be considered particularly if the heart rate is above 60 cpm as it generally does in children. Consideration of the heart rate effect on the percentile limits would require stratification by heart rate in each age subinterval, or in suitably pooled subgroups by age.

Eberle and al evaluated QT as a linear function of the RR interval in 373 healthy schoolchildren stratified into three age groups (5 to 8 years, 9 to 12 years and 13 to 16 years). The authors list the values of the predicted QT (QTp) from their regression equations is each subgroup by age and gender for heart rates from 50 cpm to 150 cpm together with the upper 5 percentile limits (QTp95). It should be noted, however, that the upper normal limits listed appear to be the 95th percentile limit of the confidence interval of the mean QTp rather than the upper 5th percentile of the QT distribution for a given heart rate.

The problem in determination of normal limits for QT interval in children is that stratification into subgroups by age and heart rate (and gender in adolescent children) will require very large study groups to achieve adequate stability of the normal QT limits.

Visual QT measurement and Validation of Computer Measurement of QT.

As well known, proper measurement of the QT interval requires identification of the earliest ECG sign of ventricular depolarization and the latest sign of the end of ventricular repolarization. QT measurements separately from various ECG leads without simultaneous consideration of other selected leads often gives misleading QT values.

Some practical guidelines for QT measurement and for validation of QT measurement by computer software are summarized in Tables 4 and 5.

Table 4. Visual QT Measurement- Some hints

- Need earliest QRS onset and latest T end.

- ➢ Generally, V2-V3, or V4-V5 will give the best T end, and usually also the earliest QRS onset.

- ➢ Use aVR if QRS onset or T offset gives problems.

Table 5. Validation of Computer-Measured QT

- ➢ A display of 3 simultaneous ECG leads is needed.

- ➢ Evaluate the best combination of 3 leads from V2-V5, aVR.

- ➢ **Caution:** Beware of QT outliers due to biphasic (pos/neg) T and U wave fusion (V1)

- ➢ With overlapping U wave, use aVR or aVL for T endpoint.

Evaluation of Prolonged Repolarization in Bundle Branch Blocks

Contrary to intuitive expectations, QRS duration has a nearly negligible effect on QT interval and upper normal limits for rate-adjusted QT as long as ventricular conduction remains normal (1). In contrast, in bundle branch blocks (QRS duration ≥120 ms), QRS duration has a strong influence on QT and QRS duration has to be taken into consideration. This can be done by incorporating QRS duration as a covariate with RR in the QT adjustment function (7), shown by Equations [6] and [7]:

[6[$QTrr,qrs = QT + 155 *(1 – RR) – 0.93*QRS - 34$ ms in women, and

[7] $QTrr,qrs = QT = 155 *(1 – RR) – 0.93 – 22$ ms in men.

In Equations [6] and [7], QTrr,qrs denotes QT adjusted for the RR interval and QRS duration. (QT and QRS are the measured QT and QRS in ms and RR in seconds).

With the above bivariate QT adjustment functions the limits for QT prolongation are the same as in normal conduction in Table 1.

An alternative, and perhaps a little simpler in practical applications is to use the JT interval for rate adjustment (7). In this case QRS duration can be omitted and the adjustment functions for women and men will take the form of Equations [8] and [9], respectively:

[8] JTrr = JT + 155*[1 – RR] + 22 ms in women, and

[9] JTrr = JT + 155*[1 – RR] + 34 ms in men.

For JT adjustment functions in Equations [8] and [9], the valid limits for JT prolongation are listed in Table 4 below.

Table 4. Practical Limits for JT Prolongation and Shortening in Bundle Branch Blocks

- JT Prolonged* 360ms
- JT Short* 370 ms

*Upper and lower second percentile limits

QT evaluation from serial ECGs

This question becomes exceedingly important in particular in the assessment of potential adverse effects of drugs in clinical trials.

Table 5. Procedural Consideration in QT Evaluation from Serially Recorded ECGs

- Strict quality control
- Identical ECG recording and QT measurement procedures
- Same electrocardiographer to perform validation of QT measurements by computer software

When is QT prolonged significantly from the baseline in serial comparison?

Annual variability of the rate- and gender- adjusted QT (QTrr) has been established in a group of 902 normal subjects (2). The upper second percentile limit for an annual QTrr increase is 32 ms. As a practical guideline, a 40 ms QTrr increase is suggested here for a significant new QT prolongation, and a 40 ms decrease as a significant new QT shortening.

Recent FDA guidelines suggest that two levels of rate-corrected QT increases from the baseline should be counted and reported in drug trials: increases 30 ms to 59 ms, and increases 60 ms and more (8).

1. Rautaharju P, Rautaharju F. Investigative Electrocardiography in Epidemiological Studies and Clinical Trials. Springer-Verlag London Limited, London, 2007.
2. Rautaharju P, Zhang ZM. Linearly Scaled, Rate-Invariant Normal Limits for QT Interval: Eight Decades of Incorrect Application of Power Functions. J Cardiovasc Electrophysiol 2002;13:1211-1218.
3. Rautaharju PM, Prineas RJ, Kadish A, Larson J, MSc, Lund B. Normal standards for QT and QT subintervals derived from a large ethnically diverse population of women aged 50 to 79 years (The Women's Health Initiative [WHI]). Am J Cardiol. 2006;97:730-737.
4. De Bruyne MC, Hoes AW, Kors JA, Hofman D, van Bemmel JH. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. Eur Heart J 1999;20:278-284.
5. Sagie A, Larson MG, Goldberg RJ, et al. An improved method for adjusting the QT interval for heart rate (the Framingham Study). Am J Cardiol 1992;70:797-801.
6. Hnatkova K, Malik M. "Optimum" formulae for heart rate correction of the QT interval. Pacing Clin Electrophysiol 1999;22:1683:1687.
7. Rijnbeek PR, Witsenburg M, Schrama E, Hess J, Kors JA. New normal limits for pediatric electrocardiogram.
8. Rautaharju PM, Zhang ZM, Prineas R, Heiss G. Assessment of prolonged QT and JT intervals in ventricular conduction defects. Am J Cardiol 2004;93:1017-1021.
9. US Department of Health and Human Services, Food and Drug Administration. Document E 14, Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Non-Antiarrhythmic Drugs. October 2005.